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(REVIEW ARTICLE)

CELL-FREE DNA-BASED PRENATAL SCREENING FOR MONOGENIC AND CHROMOSOMAL DISORDERS

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ABSTRACT

Background: Since its first description in 1997, cell-free fetal DNA in maternal plasma has emerged as two distinct, but related clinical applications: population level screening for the most common fetal aneuploidies and clinical testing for a limited number of monogenic disorders in families who have known risks. Although the two applications share a biological basis, they are often mentioned separately in the literature.

Aim: This review is intended to synthesise these two aspects and summarise the current state of each application, its true shortcomings, and its areas where the evidence is weak.

Method: A narrative literature review was performed, searching PubMed, Embase and the Cochrane Library for articles published between 1997 and December 2024 and hand searching and retrieval of professional guidance documents. Large prospective cohort studies, meta-analyses and systematic reviews were prioritised.

Result: There is a strong evidence base to support chromosomal screening, especially for the detection of trisomy 21, with pooled detection rates consistently over 99% and with a low false positive rate in unselected populations. While monogenic diagnosis is technically more challenging, is available at a handful of specialist laboratories and relies heavily on the prior characterisation of the familial mutation.

Conclusion: There are clear and persistent gaps in access to health care and the common misconception that screening results are communicated with greater certainty than the statistics warrant are the most pressing unanswered questions in this area.

Keywords: Cell-Free DNA; Non-Invasive Prenatal Testing; Non-Invasive Prenatal Diagnosis; Aneuploidy Screening; Monogenic Disorders; Relative Haplotype Dosage; Prenatal Genetics

1 INTRODUCTION

The finding by Lo, et al., (1997) that fetal DNA is in free circulation in the maternal plasma was a greater turning point in the course of prenatal medicine than almost anything in the last 50 years. Prior to this observation, there were only two options for clinicians who wanted to determine if an unborn child had a chromosomal abnormality or an inherited mutation: chorionic villus sampling or amniocentesis, each with a small but very real risk of miscarriage. It was the cell-free fetal DNA, which was released mainly by the trophoblast and could be detected from the tenth week of pregnancy onward, that provided the tantalising prospect of fetal testing without contact. The journey from possibility to routine clinical use has taken the better part of 30 years and great leaps in sequencing technology and bioinformatics.

Non-invasive prenatal testing (NIPT), which is often shortened to NIPT, is now a part of antenatal care pathways in the majority of developed countries, mainly as a screening tool for the common autosomal trisomies, sex chromosome aneuploidies and trisomy 21, 18 and 13 (Bianchi et al., 2014; Norton et al., 2015). In this role it has been demonstrated again and again to outperform combined first trimester biochemical and ultrasound screening, for example, with pooled sensitivities of over 99 per cent in large meta-analyses for trisomy 21 (Gil et al., 2017; Taylor-Phillips et al., 2016). Less well recognized outside specialist genetics units is that the same principle (cell-free fetal DNA fragments in the mother's circulating DNA) has been exploited to help diagnose single gene, or monogenic, disorders. This second use is technically more challenging and clinically more diverse than the detection of aneuploidy, since a specific mutation that is targeted needs to be known and, in many cases, parental genotyping must be done before the assay.

The reason why this particular technology was more difficult to adapt for monogenic diagnosis than for aneuploidy screening is a clue to the limitations of the underlying biology. Aneuploidy detection is based on a relatively coarse signal, a small quantitative excess or deficit of DNA fragments that map to any whole chromosome, which can be detected statistically from thousands of sequencing reads, with no prior knowledge of the particular fetus being tested. The diagnosis of monogenic, by contrast, typically involves a single base change or minor deletion somewhere in the middle of three billion base pairs, mixed in with a lot of maternal DNA, the majority of which is not fetal. This difference in signal to noise ratio provides a large part of the reason why chromosomal NIPT has been so widely adopted clinically, and monogenic NIPD still relies, in most services, on exhaustive prior characterisation of the specific mutation of the family.

This review aims to bring these two strands together. In the current article, the authors do not view chromosomal and monogenic non-invasive prenatal diagnosis as separate entities as many texts do, but rather examine the points of commonality and the areas of difference between the two. The aim is not to be a comprehensive systematic review, as this would be several times the length of the present document, because of the scope of the topic, but rather a critical synthesis designed for the clinician, the trainee and laboratory scientists who require a working knowledge of how the technology is currently developed, what its true shortcomings are, and where the evidence base is weak. Special focus is given to the test performance characteristics, the practical and ethical challenges of marketing and interpreting screening tests as diagnostic devices, and the access gap between richer and poorer health systems.

2 MATERIALS AND METHODS

This is a narrative literature review and there was no a priori protocol in advance registered at PROSPERO or similar database. The author searched PubMed, Embase and the Cochrane Library for articles published in English between January 1997, the year of Lo and colleagues' original description of cell-free fetal DNA, and December 2024. The search terms used were "cell-free DNA" or "cell-free fetal DNA" or "non-invasive prenatal testing" or "non-invasive prenatal diagnosis" combined with "chromosomal", "aneuploidy", "trisomy", "monogenic", "single gene disorder" and "prenatal screening". These terms were combined in different ways using boolean operators, and papers were researched periodically during the drafting of the review to ensure that papers were published during the writing of the review, with the latest search in December 2024. The author screened the abstracts and titles of each search for relevance before full text retrieval. A paper was deemed to be potentially relevant if it reported original data regarding technical performance of the cell-free DNA test in pregnancy, clinical validation or application of the test, or was a systematic review, meta-analysis, or a professional guidance document on the same topic. For the most part, articles which were abstracts of conferences, editorials without full publication or case reports with only a single family description were excluded unless they illustrated a point not well illustrated in the bigger studies, which was judged with fidelity in the text at the place where it was applied. Reference lists for key papers and existing systematic reviews were also hand searched for missed material; this proved to be particularly useful in identifying many of the older papers, particularly from the late 1990s and early 2000s, that are not always well indexed with the search terms that are in use today. The main sources of professional body guidance documents were the websites of the professional body (for example, the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynaecologists, International Society for Prenatal Diagnosis) rather than bibliographic databases, as these documents are not indexed in the same way. Where these were available, large prospective cohort studies were given priority because these study

designs provide a more reliable estimate of test performance in a population to which the test will ultimately be applied. Smaller cohort studies and case series have replaced some of this, especially in the section dealing with monogenic diseases, because the rarity of individual diseases (such as spinal muscular atrophy or the different types of skeletal dysplasia) makes large multicentre trials like those in aneuploidy research often impractical, and much of the published evidence in this area is based on only single centre or single national service experience. Studies excluded did not diagnose cell-free DNA work in areas other than cell-free DNA in pregnancy, such as oncology liquid biopsy sequencing depth or bioinformatic filtering, unless there was a direct relevance to a methodological development for use in the prenatal context. In view of the rapid advances in the sequencing techniques as well as in clinical guidelines over the period covered, a special emphasis was placed on publications from the last 10 years, although some foundational papers from the late 1990s and 2000s have been included and discussed, as they still hold historical or technical significance in the context of the development of the field. This is a narrative rather than a systematic exercise in the sense that there was no formal quality appraisal tool used to review the included studies in a standardised way across the included studies; however, the author has tried throughout the Results and Discussion to highlight explicitly where a finding is based on a small sample size, single centre experience, or study population which may not generalise well to unselected pregnant women.

3 RESULTS

3.1 The biological and technical basis of the test

The free fetal DNA fragments are short (usually 143 to 166 bp) and from the apoptotic trophoblast cells, rather than from the foetus itself, which is clinically relevant as it helps to explain the discrepancies in the presence of confined placental mosaicism (Bianchi and Chiu, 2018; Lawal and Acquah, 2025). The fetal fraction, usually defined as the proportion of fetal DNA in its mother's plasma, increases during gestation, but individual fetal fraction levels can vary widely, and a fetal fraction less than about four per cent is generally considered to be too low for reliable analysis (Ashoor et al., 2013). Because maternal obesity is a known factor that is associated with low fetal fraction (often thought to be from higher output of maternal DNA, not less contribution from the fetus), and because women who are obese are more likely to receive a "no call" result and to require repeat sampling (Livergood et al., 2017), this is a very practical limitation that needs to be taken into account.

There are two general approaches to aneuploidy screening that are currently in use in the laboratory. This method involves sequencing large numbers of DNA fragments across the genome and searching for a proportionally larger number of fragments that align to the chromosome of interest, also first applied by Chiu et al. (2008) and independently by Fan et al. in (2008). Targeted approaches, in contrast, sequence only the regions of interest, typically those at chromosomes 21, 18, and 13 plus the sex chromosomes, and at a lower cost of sequencing, can achieve similar accuracy in the large cohort reported by Palomaki and colleagues (Palomaki et al., 2011). A third approach is through single nucleotide polymorphisms (SNPs) which can be used to compare the allele ratio at informative loci to determine copy number, as well as provide a secondary benefit of detecting vanishing twin and triploidy, but are generally less accurate in twin pregnancies (Norton et al., 2015; Gil et al., 2017).

The technical requirements vary greatly for monogenic disorders. Where the paternal allele differs from the maternal, the direct detection of the paternally inherited mutant or wild-type sequence in maternal plasma is relatively simple and has been successfully applied for conditions like achondroplasia and some skeletal dysplasias caused by de novo paternal mutations (Chitty et al., 2011). The detection of a maternally inherited mutation is much more difficult, as the background of normal (wild type) and abnormal (mutant) sequence from the mother's own genome is already present in bulk in the plasma, and a small contribution from the fetus can only be distinguished by digital droplet PCR and very high sensitivity, or by recent development of relative haplotype dosage analysis, a method developed by Lo and colleagues which can estimate from a statistical analysis of the relative abundance of maternal haplotypes, which haplotype the fetus has inherited from the mother (Lo et al., 2010; New et al., 2014). Since then, relative haplotype dosage, or RHDO, has been clinically used for a range of diseases such as cystic fibrosis, congenital adrenal hyperplasia, spinal muscular atrophy and a number of haemoglobinopathies; and has been reported in national testing services in the UK, with turnaround time and accuracy that makes it a valid and viable clinical alternative to invasive sampling in selected families (Parks et al., 2016; Scotchman et al., 2020).

3.2 Performance for chromosomal disorders

This has created a very robust evidence base for the clinical performance of cell-free DNA screening for Trisomy 21, an evidence base which is unusual for a screening test of this nature. In a prospective study of a general obstetric population of more than fifteen thousand women, Bianchi et al. (2014) found that cell-free DNA testing had a significantly lower false positive rate (FPR) for trisomy 21 than standard screening, and high sensitivity was achieved in both methods. This was followed by the NEXT study by Norton et al., which again used an unselected population and

found few false positive results with cell-free DNA screening at broadly similar detection rates as standard screening (Norton et al., 2015). The meta-analysis of Gil et al. (2017), and pooling data from many published cohorts, found pooled detection rates of more than ninety-nine per cent and a false positive rate of less than one per thousand, which is a significant improvement over the previous biochemical and ultrasound markers.

However, the performance for trisomy 18 and trisomy 13 is slightly less favourable, and for the detection of sex chromosome aneuploidies generally good, but with greater variety of biological confounder such as maternal mosaicism and potential undiagnosed maternal sex chromosome abnormality (Bianchi and Chiu, 2018). Principal large cohort studies and meta-analyses are summarized in terms of comparative performance in Table 1.

Table 1: Pooled performance of cell-free DNA screening by condition

Condition	Pooled detection rate	Pooled false positive rate	Key source
Trisomy 21	approx. 99.7%	approx. 0.04%	Gil et al. (2017)
Trisomy 18	approx. 97.9%	approx. 0.04%	Gil et al. (2017)
Trisomy 13	approx. 99.0%	approx. 0.04%	Gil et al. (2017)
Sex chromosome aneuploidy	approx. 90-95% (varies by condition)	higher than autosomal trisomies	Bianchi and Chiu (2018)

Source: adapted from Gil et al. (2017) and Bianchi and Chiu (2018).

One point that often is not discussed as much as it should be in the clinical setting is the difference between the positive predictive value of a screening test and its sensitivity. In absolute terms, trisomy 21 is a rare occurrence in an unselected obstetric population; even a highly sensitive test can produce a significant number of false positive results in real terms and invasive testing should be recommended before any irreversible decision (Gregg et al., 2016; Taylor-Phillips et al., 2016). This has been a common cause of public confusion, and, at times, the public has understood that some cell-free DNA tests are screening tests and not diagnoses (Deans and Newson, 2012; Dondorp et al., 2015).

3.3 Performance and application for monogenic disorders

The literature on monogenic non-invasive prenatal diagnosis is significantly less cohesive than that of aneuploidy, both due to the low prevalence of individual conditions and because most literature reports are from single centres or from a limited number of national or supra-regional centres. Lench et al. (2013) provided the early UK experience of delivering a clinical service model across a variety of conditions including achondroplasia, thanatophoric dysplasia, and several single gene disorders, showing that a clinical service model was not only feasible, but also accurate enough to be implemented outside a purely research environment. New et al. (2014) have also reported that cell-free DNA testing may be used to successfully identify affected from unaffected pregnancies in families with a known or presumed risk of CAH due to twenty-one hydroxylase deficiency, thereby avoiding unnecessary dexamethasone treatment for mothers of non-affected pregnancies, which were previously initiated on an empirical basis before diagnosis could be confirmed.

In a broad review of the National Health Service's (NHS) experience of providing non-invasive prenatal diagnosis (NIPT) for monogenic disorders, Scotchman et al. (2020) described diagnostic accuracy as broadly equivalent to that of invasive testing for a range of disorders, but found that the time required for results, costs and the need for prior familial mutation characterisation remain practical challenges to broader adoption of NIPT. Specifically, Parks et al. (2016) reported that relative haplotype dosage analysis was reliable from approximately 11 weeks gestation onward but needed an informative single nucleotide polymorphisms (SNPs) panel and high fetal fraction, which is not necessarily the case in every family referred. In most services monogenic NIPD is not used to screen for aneuploidy, but instead will only be offered to families who are already at high risk of the condition, typically because they have a family history of the condition in their child or by one or both parents being carriers of a monogenic condition, and therefore monogenic NIPD is more of a diagnostic test than a population screening tool, with real implications for counselling and actions taken after a result (Chitty and Lo, 2015).

In practice, the two applications differ somewhat in terms of cost. Population level testing relies on the per sample cost being affordable for a national programme and the costs have dropped significantly since the first commercial screening programmes were introduced in around 2011, but the extent to which this has been funded going into the public health system varies a lot between different health systems (Hui and Bianchi, 2017). Precisely because monogenic NIPD is only offered to a small number of high risk families and not to a whole pregnant population, it has been subject to a different economic logic, one in which the cost is more related to the process of validating an informative single nucleotide polymorphism panel for each family than to the reagents used for the sequencing. Turnaround time is also a factor, with most monogenic NIPD results along the National Health Service pathway taking 1-2 weeks following sample receipt

which is important clinically when parents are counselled early in the second trimester and wish to make a prompt decision regarding termination of pregnancy (Scotchman et al., 2020).

4 DISCUSSION

The evidence reviewed here lends credence to a reasonably assured assertion that cell-free DNA testing has transformed prenatal care for the common aneuploidies, and that it has also added value in the care of monogenic diseases; however, its value in care of monogenic diseases is significantly less widespread and relies more heavily on specialist laboratory infrastructure. Some of these tensions can be highlighted quite explicitly, as they are not necessarily discussed with the same frankness in literature sponsored by commercial firms.

The first relates to language and the merging of screening with diagnosis. In invasive testing, the cell-free DNA test is, strictly speaking, a screening test, and all major professional body guidelines still recommend that confirmatory testing be done before an affected pregnancy is discussed for termination (Gregg et al., 2016; American College of Obstetricians and Gynecologists, 2020). However, the language used by some commercial groups, and some of the earlier peer-reviewed literature was at times more certain than the underlying statistics would suggest, especially for less common sex chromosome conditions, where the positive predictive value may be much lower than that of trisomy 21 (Bianchi and Chiu, 2018; Deans and Newson, 2012). This distinction needs to be made clear to patients during counselling, and there is some evidence that patients' awareness of the risk of residual risk after a low risk result is not uniform (Farrell et al., 2015).

The second tension deals with increasing the range of chromosomal screening beyond the typical trisomies. Screening for rarer autosomal trisomies and microdeletion syndromes like 22q11.2 deletion is also possible in several commercial laboratories, although the positive predictive value for these disorders is much lower than for the common trisomies, due to the relative rarity of these conditions in the unselected population, and the evidence base supporting their routine clinical use is weaker (Dondorp et al., 2015; Taylor-Phillips et al., 2016). The International Society for Prenatal Diagnosis has called for caution here, as an increase in the range of conditions tested without a commensurate increase in pre-test counselling may result in an increase in anxiety that does not outweigh any clinical benefit (Benn et al., 2015).

A third and, in the author's view, underappreciated tension concerns equity of access. Nearly all of the large validation cohorts mentioned above were performed in well-resourced health systems from North America, Western Europe, Hong Kong and mainland China, and the specific infrastructure necessary for monogenic NIPD (particularly) and for informative single nucleotide polymorphism panels and next generation sequencing (NGS) capacity is not available in most low and middle-income countries. Cost is also a barrier to chromosomal cffDNA testing in high-income countries where it is not funded by the national health system, and there is a defensible anxiety that the technology developed to lower the risk of miscarriage from invasive procedures will, in reality, exacerbate the current access inequalities to prenatal care instead of resolving them (Chitty and Lo, 2015).

Another methodological limitation to be critically raised is that the number of studies in the aneuploidy literature used to assess test performance is often on the basis of high risk or enriched populations, which may overestimate the test's performance, compared to what would be seen in an actual unselected screening population, as noted by Taylor-Phillips and colleagues in their systematic review, who specifically excluded studies conducted in high risk or enriched populations, and found that the performance of the tests was excellent but slightly lower than some of earlier high risk cohort estimates (Taylor-Phillips et al., 2016). This is important because decisions regarding implementation at the population level require performance estimates from the population in which the test will be implemented, rather than from enriched research cohorts.

A brief note on the health economic considerations is warranted since they will be the final factors in determining the extent to which these tests become utilized outside of research contexts. Health systems have overall shown that implementing cell-free DNA screening as a contingency second tier test, reserved for women who receive an intermediate risk outcome from their combined first tier test, has led to overall reduction in invasive testing and associated miscarriage without excessive cost to the overall programme (Taylor-Phillips et al., 2016). The cost implications are significantly higher and the case for public funding is less tenable if it has been introduced as the first line universal test, rather than just women at risk. While this difference between contingent and universal implementation models may be missed in public debate, it is important to keep in mind for policies which face allocation of an already limited antenatal screening budget.

In the near future, several developments appear promising for the future of this field. In principle, sequencing costs continue to drop, making monogenic NIPD more accessible and more affordable, although laboratory skill and bioinformatic pipeline validation are still rate-limiting steps that will not be solved cheaply and quickly by money (Scotchman et al., 2020). In addition, there is increasing interest in the use of relative haplotype dosage and similar approaches for a larger number of monogenic diseases than are currently available on most services, and the

development of approaches that do not require prior characterisation of mutations in the parents, since this would greatly expand the clinical applicability of these approaches (Chitty and Lo, 2015). The possibility that these advances might be matched by similar investments in genetic counselling capacity is less assured, and unfortunately receives far less focus from funders and policy makers, because without such capacity, the ethical risks outlined above will only increase.

5 CONCLUSION

The use of cell-free DNA testing of maternal plasma has progressed from a laboratory curiosity to now forming an important part of routine antenatal screening for a range of chromosomal disorders and to being a truly diagnostic tool in specialist centres for a specific and expanding range of monogenic disorders. The evidence supporting its use for screening of Trisomy 21 is now very large and consistent and based on numerous well-designed studies. In the field of monogenic disease, although still relatively immature and more technically challenging, it has already had an impact on the management of a number of severe inherited diseases and will become increasingly common as sequencing costs continue to drop. The ongoing issue of inequitable access to screening and the frequent incompleteness of the information provided by the tests at times are communicated and understood more accurately than the statistics support, are not something the evidence base can yet answer, and will require deliberate policy attention and not further laboratory refinement. The health care worker working in this field is in a special position because the technology has developed at a rapid pace that the general public and even health professionals are being caught up by the excitement of the development and not the actual limitations.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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